FDA ADVISORY COMMITTEE:
Neonatal Opioid Withdrawal Syndrome

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June 8, 2015

The UNIVERSITY of VERMONT

THE University of Vermont Children's Hospital

Disclosures:

- I will discuss off-label uses of medications
- I have no financial disclosures

However, I am a Canadian, eh?

Neonatal Opioid Withdrawal Syndrome (NOWS): Objectives

- Historical context
- Current context
- Pathophysiology
- Signs and symptoms of NOWS
- Factors affecting the incidence and severity of NOWS
- Management
- Outcomes
- UVM Experience

NOWS: Description

- Neonatal Abstinence Syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome (NOWS) often results when a pregnant woman uses opioids (e.g., heroin, oxycodone) during pregnancy.
- Defined by alterations in the:
  - *Central nervous system*
    - high-pitched crying, irritability
    - exaggerated reflexes, tremors and tight muscles
    - sleep disturbances
  - *Autonomic nervous system*
    - sweating, fever, yawning, and sneezing
  - *Gastrointestinal distress*
    - poor feeding, vomiting and loose stools
  - *Signs of respiratory distress*
    - nasal stuffiness and rapid breathing

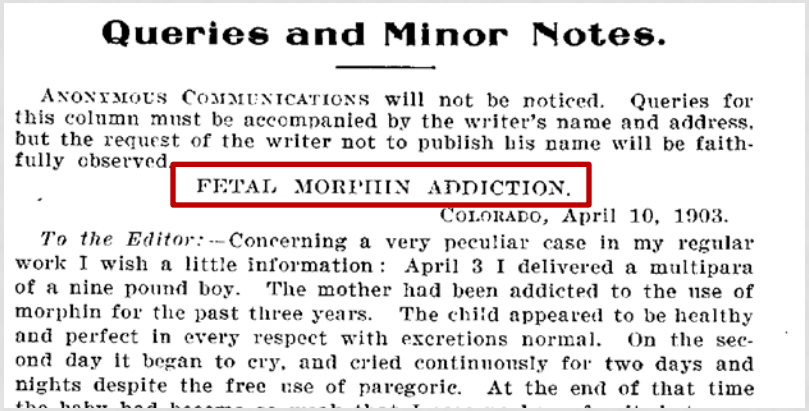
- **NAS is *not* Fetal Alcohol Syndrome (FAS)**
- **NAS is treatable**

Slide courtesy of H Jones

(Finnegan et al., *Addict Dis*. 1975; Desmond & Wilson, *Addict Dis*. 1975)

NOWS: Historical Context

- 1875 to 1900 multiple reports of congenital morphinism – most died, no specific treatment offered
- 1903 report about congenital morphinism –treated infant with morphine
- 1964 Methadone introduced as pharmacotherapy
- 1965 Goodriend et al report neonatal withdrawal signs
- 1971 Zelson et al reported frequency of signs on neonatal withdrawal in 259 of 384 infants born to drug-abusing mothers
- 1975 Desmond and Wilson publish Neonatal Abstinence Syndrome: Recognition and Diagnosis
- 1975 Finnegan et al publish neonatal abstinence syndrome tool



Queries and Minor Notes.

ANONYMOUS COMMUNICATIONS will not be noticed. Queries for this column must be accompanied by the writer's name and address, but the request of the writer not to publish his name will be faithfully observed.

FETAL MORPHIN ADDICTION.

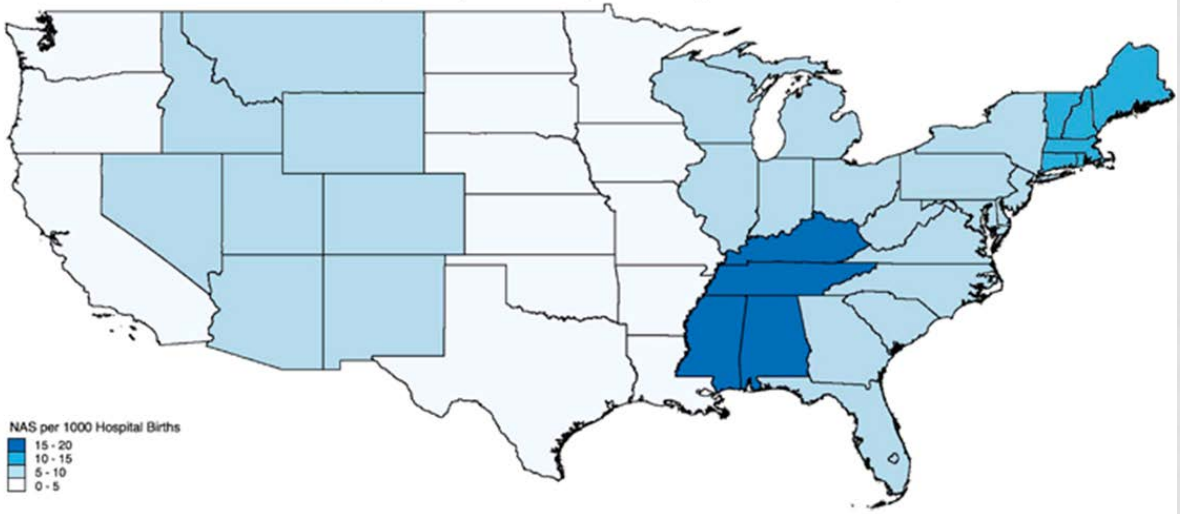
COLORADO, April 10, 1903.

To the Editor:—Concerning a very peculiar case in my regular work I wish a little information: April 3 I delivered a multipara of a nine pound boy. The mother had been addicted to the use of morphin for the past three years. The child appeared to be healthy and perfect in every respect with excretions normal. On the second day it began to cry, and cried continuously for two days and nights despite the free use of paregoric. At the end of that time

JAMA, 1903

Musee d'Albert Kahn, Leon Busy, 1915

NOWS: Current Context



US Census Division	NAS Rate per 1000 Births (95% CI)
New England	13.7 (12.5-14.5)
Middle Atlantic	6.8 (5.9-7.6)
East North Central	6.9 (6.0-7.8)
West North Central	3.4 (3.0-3.8)
South Atlantic	6.9 (6.3-7.4)
East South Central	16.2 (12.4-18.9)
West South Central	2.6 (2.3-2.9)
Mountain	5.1 (4.6-5.5)
Pacific	3.0 (2.7-3.3)

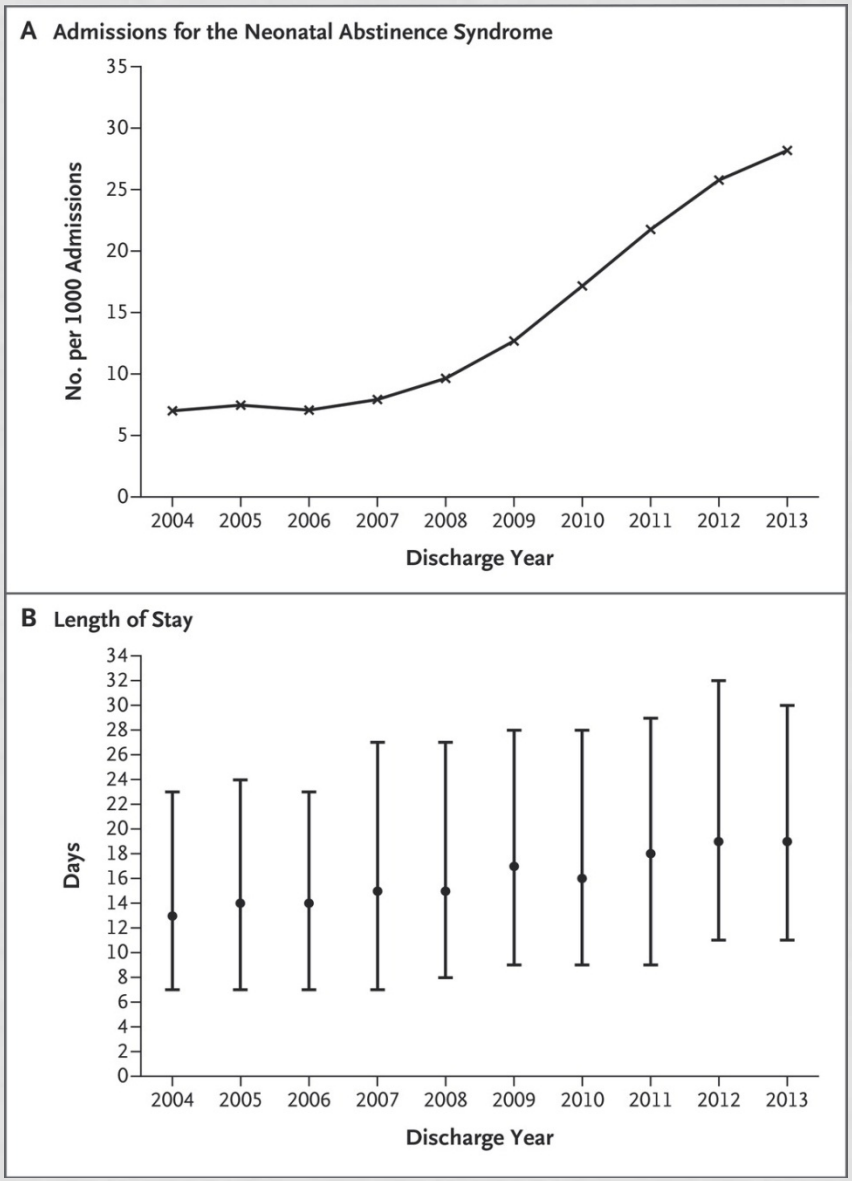
2012:

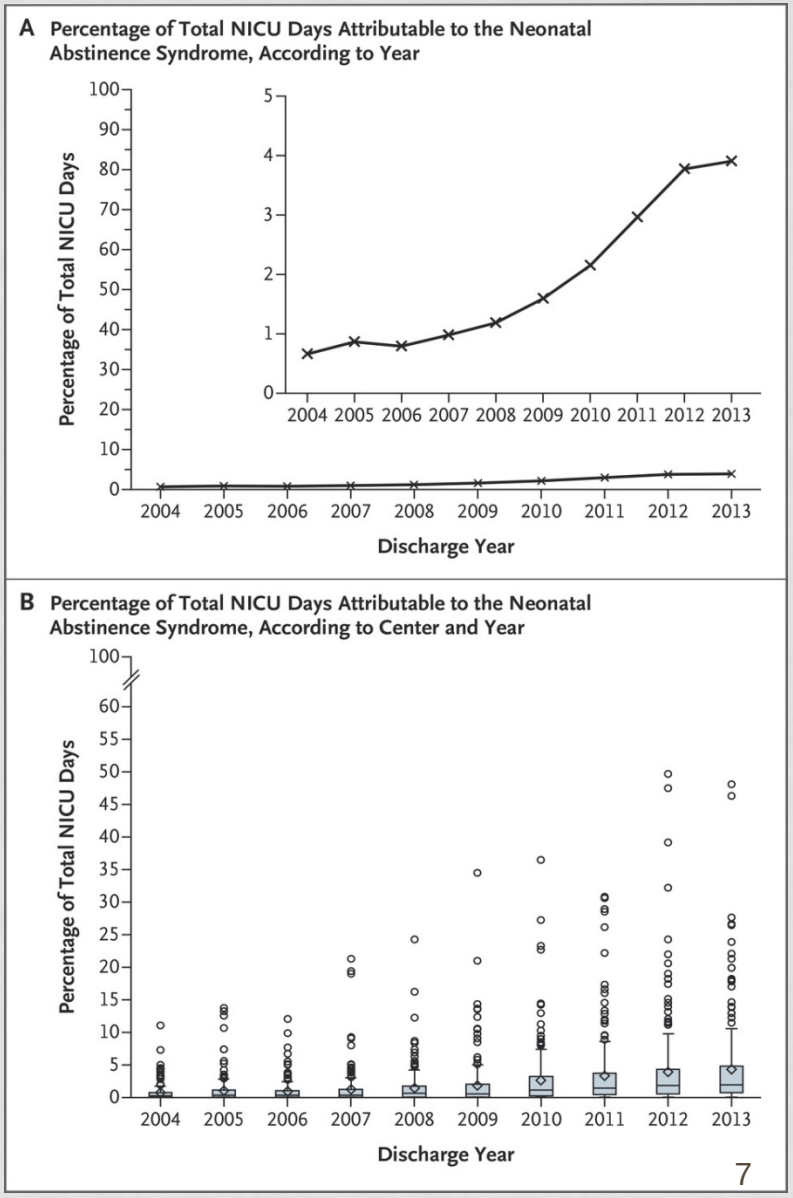
- 21,732 newborns
- ~$1.5 billion
- 81.5% Medicaid
- ↑ complications

Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012
Patrick et al, J of Perinatology, 2015

The NEW ENGLAND JOURNAL of MEDICINE

TOLIA VN ET AL. N ENGL J MED 2015;372:2118-2126.





NOWS: Current Context

Issues facing substance-using pregnant women and their children

- Generational substance use
- Gender inequality/male-focused society

- Legal involvement
- Unstable housing
- Unstable transportation

- Limited parenting skills and resources
- Exposure to trauma

- Lack of positive and supportive relationships

Slide courtesy of H Jones

The untreated woman with opioid-use disorder who becomes pregnant: neonatal effects

- Neonatal opioid withdrawal
- Neonatal complications
  - Meconium aspiration, transient tachypnea
  - Feeding difficulty, seizures, jaundice
- If recognized that mother is opioid-dependent
  - Child protective services involvement
  - Challenge of taking care of newborn and starting treatment for addiction

www.thefix.com

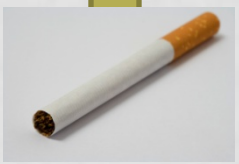
- If unrecognized and infant exhibits no withdrawal
  - After discharge infant may be particularly irritable
  - Family's ability to cope and seek help impeded by fear of discovery
  - Mother will probably remain active in her addiction
  - Exposure of infant to unsafe situations
  - Mother continuously "flying under the radar" and hiding her addiction
  - Mother often unwilling to come forward for fear of losing her child / children

Medication Assisted Treatment (MAT): Standard of Care for Pregnancy

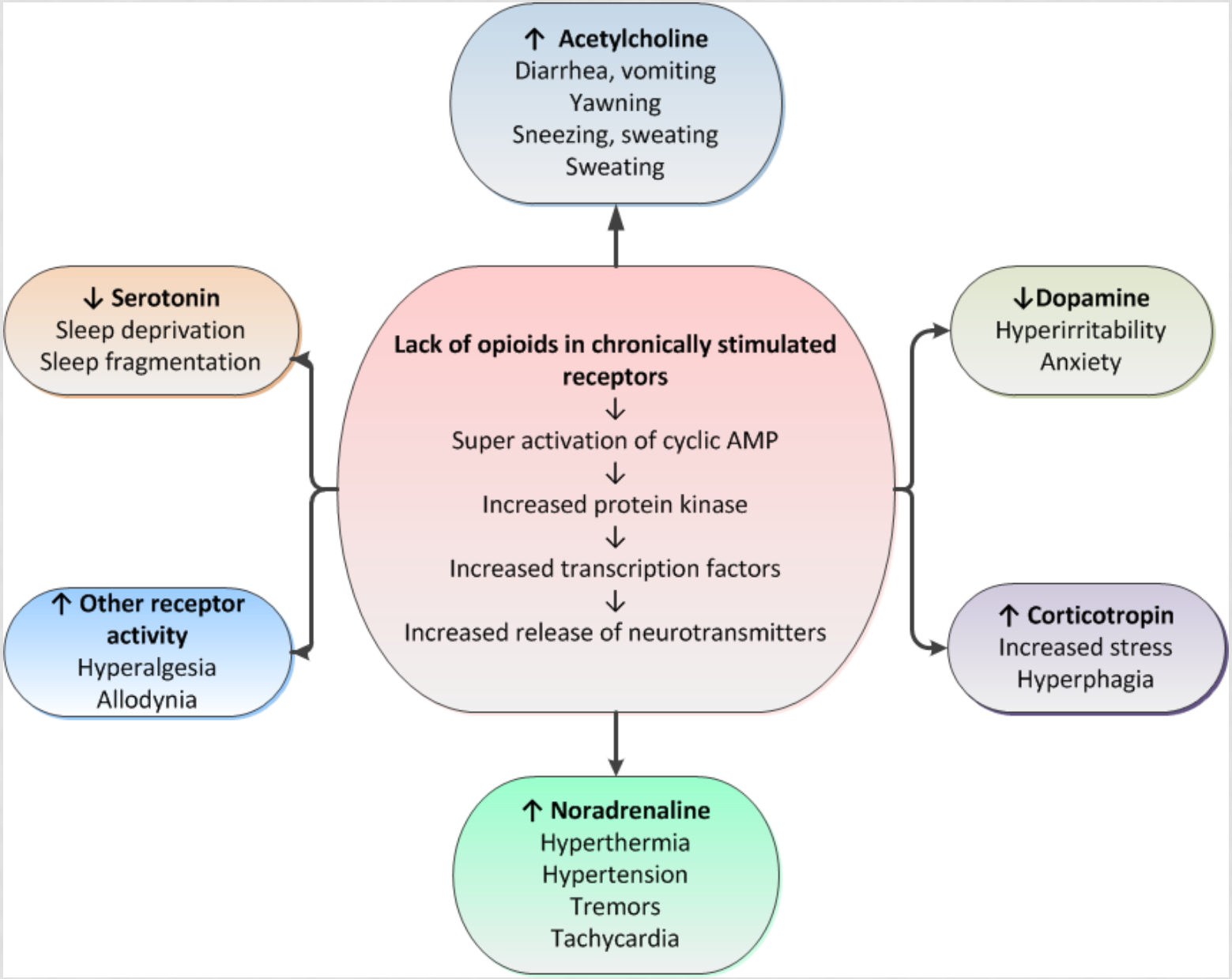
- WHO 2014: “Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment…rather than…attempt opioid detoxification.”
- Facilitates retention of mothers/infants with decreased use of illicit substances when compared to no medication
- MAT results in NOWS which needs Rx in 50-60% patients (Jones et al, 2010)
- There is no evidence for the dose of methadone affecting the incidence of NOWS (Cleary et al, 2010; Jones et al., 2013)

NAS ≠ NAS ≠ NAS

NAS Profile



Pathophysiology of Neonatal Opioid Withdrawal



Adapted from Prabhakar Kocherlakota Pediatrics 2014;134:e547-e561

NOWS: Signs and Symptoms

- Signs of withdrawal typically start after 24-96 hours after birth depending upon the specific opioid exposure
- Central nervous system signs
  - Tremors
  - Irritability, high-pitched crying
  - Sleep disturbances
  - Tight muscles tone, hyperactive reflexes
  - Myoclonic jerks (sometimes misinterpreted as seizures), seizures - rare
- Autonomic signs
  - Sweating, fever, yawning and sneezing
  - Rapid breathing, nasal congestion
- Gastrointestinal signs
  - Poor feeding, vomiting and loose stools or diarrhea

What would happen if NOWS is untreated?

- Depends upon the severity
- There are many infants who do not receive medication for NOWS and their outcome is good
- However, an irritable, crying baby who does not sleep and cannot feed will be at risk for
  - Dehydration
  - Abusive trauma
  - Interrupted attachment and maybe failure of attachment
- Excessive irritability and dehydration are very likely to lead the caregiver to seek medical attention
- An infant may die without treatment – however, in an extensive literature search, the only reported deaths occurred over 100 years ago
- NOWS does not lead to poor neurodevelopmental outcomes

Scoring tools for NOWS/NAS

- Finnegan Neonatal Abstinence Scoring System
  - 31 items
  - Symptoms are weighted
  - Guidelines for pharmacologic treatment at score of 8 or greater
- MOTHER score (modified Finnegan score)
  - 19 items (which contribute to total score)
  - Items weighted differently
  - Some items eliminated and others added
  - Guidelines for treatment based on score rather than weight
- Lipsitz Neonatal Drug-Withdrawal Scoring System
  - 11 items
  - Items scored for severity and gives guidelines for treatment
- The Neonatal Withdrawal Inventory – 8 point checklist
- The Neonatal Narcotic Withdrawal Index – 6 signs plus others

NAS Assessment: MOTHER NAS Scale

Appendix Figure 2. Maternal Opioid Treatment: Human Experimental Research (MOTHER) Neonatal Abstinence Measure

PATIENT ID#_____

Dose given q 3-4 hrs with feeds; do not exceed 4 hrs between doses

SCORE Morphine (0.04mg/0.1ml) DOSE FOR INITIATION

0-8	0	
9-12	0.04	mg/dose
13-16	0.08	mg/dose
17-20	0.12	mg/dose
21-24	0.16	mg/dose
25 or above	0.20mg/dose	

Morphine Initiation:

- If neonate scores 9-12 re-score after feeding or within the hour and if re-score is 9-12 start treatment based on highest score. If re-score is 0-8, do not initiate treatment.
- If initial score is 13 or greater, start treatment immediately without reassessment.

Morphine Maintenance

- Maintain dose if score 0-8
- Increase dose by 0.02 if score is 9-12 (rescore before dosing)
- Increase dose by 0.04 if score 13-16
- Increase score by 0.06 if score 17-20

Weaning Instructions:

- Maintain on dose 48 hrs before starting weaning
- Wean 0.02 mg morphine every day for a score is 0-8
- Defer wean for score e 9-12

Re-escalation

- If neonate scores 9-12 re-score as described for initiation ,
- If second score is in 9-12 increase morphine 0.01 mg q3-4 hrs
- If 2 consecutive scores 13-16, increase 0.02 mg q3-4 hrs
- If 2 consecutive scores in 17-20, increase 0.04 mg q3-4 hrs etc

Timing of Scoring: Hospitalized infants scored every 3-4 hrs **before** feeds. Reassessment Occurs immediately **after feeds** or within 1 hour.
Discharged (e.g., in GCRC) infants scored twice a day scores must be separated by 8 hrs)
****NOTE: Discharged infants are to be admitted to hospital if the infant receives a single score of 9 or more****

SIGNS AND SYMPTOMS Please note **presence (pr) or absence (ab)** of items where indicated. Include observations for the past 4 hour period.	Score	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time	Date/time
Crying: excessive high pitched Crying: Continuous high pitched	**2** **3**								
Sleeps < 1 hour after feeding Sleeps < 2 hours after feeding Sleeps < 3 hours after feeding	**3** **2** **1**								
Hyperactive Moro Reflex Markedly Hyperactive Moro Reflex	**1** **2**								
Mild Tremors: Disturbed Moderate-Severe Tremors: Disturbed	**1** **2**								
Mild Tremors: Undisturbed Moderate-Severe Tremors: Undisturbed	**1** **2**								
Myoclonic jerks	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Increased Muscle Tone	**1-2**								
Excoriation (indicate specific area):	**1 - 2**								
Mottling	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Generalized Seizure (or convulsion)	**8**								
Convulsions	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Fever ≥ 37.3 C (99.2 F)	**1**								
Fever >38.4 (101.2 F)	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Frequent Yawning (4 or more successive times)	**1**								
Sweating	**1**								
Nasal Stuffiness	**1**								
Sneezing (4 or more successive times)	**1**								
Tachypnea (Respiratory Rate> 60/min)	**2**								
Retractions	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Nasal flaring	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Poor Feeding	**2**								
Excessive sucking	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Vomiting (or regurgitation)	**2**								
Projectile vomiting	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Loose Stools	**2**								
Watery Stools	present/absent	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab	❑pr ❑ab
Failure to Thrive (Current weight ≥ 10% below birth weight) 90% BWT=_____	**2** (record weight in score box 1 x day)								
Excessive Irritability	**1 - 3**								
TOTAL SCORE									
CURRENT MORPHINE DOSE	Dose in mg Time Given								
STATUS OF TREATMENT*	N, I, M, W, R								
INITIALS of SCORER									

Note: Code Status of Treatment as follows: N="No treatment", I="Initiation", M="Maintenance", W="Weaning", R=" Re-Escalation"

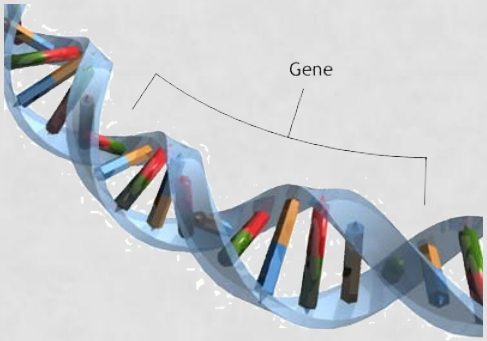
- NAS score is not the sole determining factor in the decision to start starting Rx
- Score can be affected by
  - State of infant
  - Painful stimuli
  - Order of score
  - "Motive" of scorer

Courtesy of H Jones

Factors affecting NOWS

- Substances
  - Nicotine
  - Benzodiazepines
  - SSRIs

- Single gene polymorphisms



- Hospital protocols and education of the staff, breastfeeding support

www.simplymotherhood.com

NOWS: Management

- Admit to Mother/Baby Unit – rooming-in if possible
- Minimum stay of 4-5 days to allow for symptoms to peak (onset of withdrawal in buprenorphine exposed infants is later than with methadone exposed infants)
- Utilize non-pharmacologic treatment as available
- Encourage breastfeeding
- Encourage mother to participate in the assessment of the newborn
- Role of drug testing in the infant (?)
- Crucial: excellent multidisciplinary communication

NOWS: Non-pharmacologic Treatment

- Breastfeeding is associated with reduced severity of withdrawal, delayed onset, decreased need for Rx (Abdel-Latif et al, 2006)
- Rooming-in decreased the need for Rx, length of Rx, and LOS (Abrahams et al, 2007)
- Water beds decreased amount of medication needed (Oro et al, 1988)
- Acupuncture (Filippelli et al, 2012)
- Kangaroo therapy or skin to skin
- Decreased environmental stimuli
- Frequent small demand feeds
- Pacifiers
- Swaddling, containment, holding, vertical rocking
- Provider, nursing attitudes

www.susquehannahealth.org

www.simplymotherhood.com

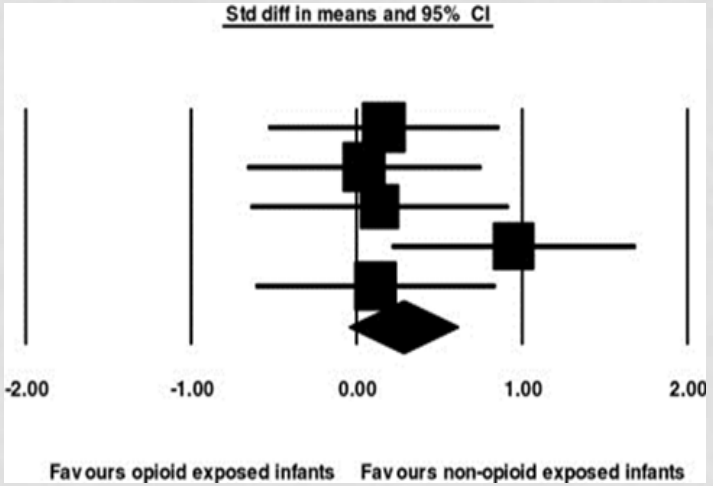
NOWS: Pharmacologic Treatment

- Short-acting opioids (morphine sulfate, dilute tincture of opium)
  - Inpatient treatment
  - “standard of care”
  - Symptom based versus weight based
  - Endorsed by the AAP (2012)
- Methadone
  - Inpatient treatment and inpatient to outpatient treatment
  - Symptom versus weight based
  - Allows for shorter length of stay (with outpatient treatment)
  - Endorsed by the AAP (2012)
  - (Several studies including MS Brown et al (2015) which revealed shortened duration of treatment with methadone)
- Dilute tincture of opium and phenobarbital (Coyle et al, 2002)
  - Decreased severity of withdrawal, decreased length of stay
- Buprenorphine (Kraft et al, 2011)
  - Shorter length of stay in buprenorphine treated infants
  - Well tolerated
- Adjunctive therapy with clonidine (Agthe et al, 2009)
  - Oral clonidine as adjunct to short-acting opioids
  - Shortens the duration of therapy, no short-term cardiovascular side effects were observed

Outcomes: Baldacchino et al, BMC Psychiatry 2014

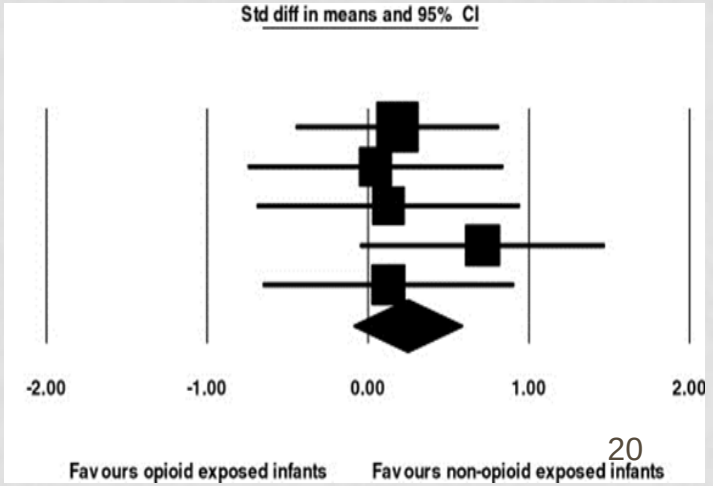
Psychomotor in opioid and non-opioid exposed infants

Study Name	Subgroup	Assessment
Hunt (2008)	1.5 years old	BSID (Psychomotor)
Burlowski (1998)	1 year old	GDS (Locomotor)
Moe (2002)	1 year old	BSID (Psychomotor)
Hans (2001)	1 year old	BSID (Psychomotor)
Hans (2001)	2 years old	BSID (Psychomotor)



Cognition in opioid and non-opioid exposed infants

Study Name	Subgroup	Assessment
Hunt (2008)	1.5 years old	BSID (Mental)
Burlowski (1998)	1 year old	GDS (DQ)
Moe (2002)	1 year old	BSID (Mental)
Hans (2001)	1 year old	BSID (Mental)
Hans (2001)	2 years old	BSID (Mental)



Outcomes: Baldacchino et al, BMC Psychiatry 2014

Cognition in opioid and non-opioid exposed infants

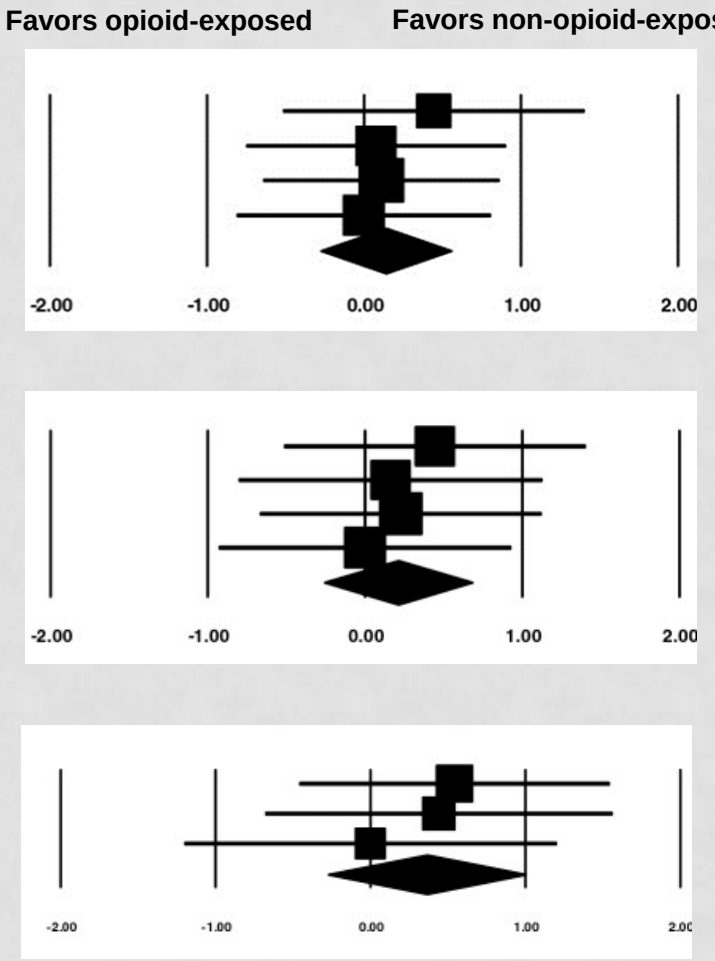
Study Name	Subgroup	Assessment
Hunt (2008)	3 years old	McCarthy
Ornoy (2001/2003)	5 years old	McCarthy
Moe (2002)	4.5 years old	McCarthy
Walhord (2007)	4.5 years old	McCarthy

Psychomotor in opioid and non-opioid exposed infants

Study Name	Subgroup	Assessment
Hunt (2008)	3 years old	McCarthy Motor Scale
Ornoy (2001/2003)	5 years old	McCarthy Motor Scale
Moe (2002)	4.5 years old	McCarthy Motor Scale
Walhord (2007)	4.5 years old	McCarthy Motor Scale

Behaviour in opioid and non-opioid exposed infants

Study Name	Subgroup	Assessment
Hunt (2008)	3 years old	Vineland Social Maturity
Ornoy (2001/2003)	5 years old	Achenbach
Moe (2002)	4.5 years old	Achenbach



New York Times

In Annual Speech, Vermont Governor Shifts Focus to Drug Abuse

By Katherine O. Seelye Jan 8, 2014

Rolling Stone

By David Amsden April 3, 2014

The explosion of drugs like OxyContin has given way to a heroin epidemic ravaging the least likely corners of America – like bucolic Vermont, which has just woken up to a full-blown crisis

By DAVID AMSDEN

The New Face of Heroin

PHOTOGRAPH BY FREDRIK BRODEN

EVE RIVAIT RODE HER FIRST HORSE WHEN SHE WAS FIVE, too small to get her feet through the stirrups, let alone give the animal a kick that registered. Yet even then, bouncing in the saddle, she was aware that being on the back of a horse provided relief from the boredom and isolation that, for her, were a more dominant part of growing up in Vermont than the snowcapped mountains and autumn foliage that draw millions of tourists to the state each year. As Eve got older, she began spending afternoons exercising the herd at Misty Ann Stables, not far from her home in Milton, a working-class town of about 10,000 located along Lake Champlain, some 30 minutes north of Burlington. Before she could drive a car, Eve was training horses at various barns in the area.

UVM Children's Hospital
Antenatal Visit With Neonatology

- Schedule 1 – 2 visits with NeoMed Clinic staff
- Written information (Care Notebook)
- http://www.uvm.edu/medicine/vchip/?Page=ICONcarenotebook.html
- **Promote breastfeeding**

UVM Children's


"I SWEAR TO TELL THE TRUTH, THE WHOLE TRUTH, AND NOTHING BUT THE TRUTH, FROM MY PERSPECTIVE."

UVM Children's Hospital
NeoMed Experience

- Alleviation of fear
  - Care Notebook
  - You are not alone…
  - Ask them for their stories
- Respect
  - Introductions to others on the team
  - "Tell me about yourself"
  - "What are your dreams / goals"
- Recognition of strengths
  - Hearts

UVM Children's Hospital
Why methadone for treatment of neonatal abstinence syndrome?

- Decreased frequency of dosing
- Less respiratory depression
- Less need for adjustment of dose

UVM Children's Hospital
Benefits /risks of newborn outpatient treatment program with methadone

Benefits

- Length of stay reduced
- Slow wean of methadone reduces symptoms of withdrawal
- Allows for more breastfeeding success
- Empowers family

Risks

- Safety concerns – overdose to baby, use by others
- Long half-life may lead to "overmedication" in hospital
- Often prolonged course – are we treating normal baby irritability with methadone?

Infrastructure: what works in Vermont

- Clinic staff with ability to “track infants down”
- Close relationships with obstetrics, substance abuse treatment providers, WIC, child protective services and home health nursing
- Single pharmacy to dispense methadone

UVM Children's Hospital
NeoMed Clinic

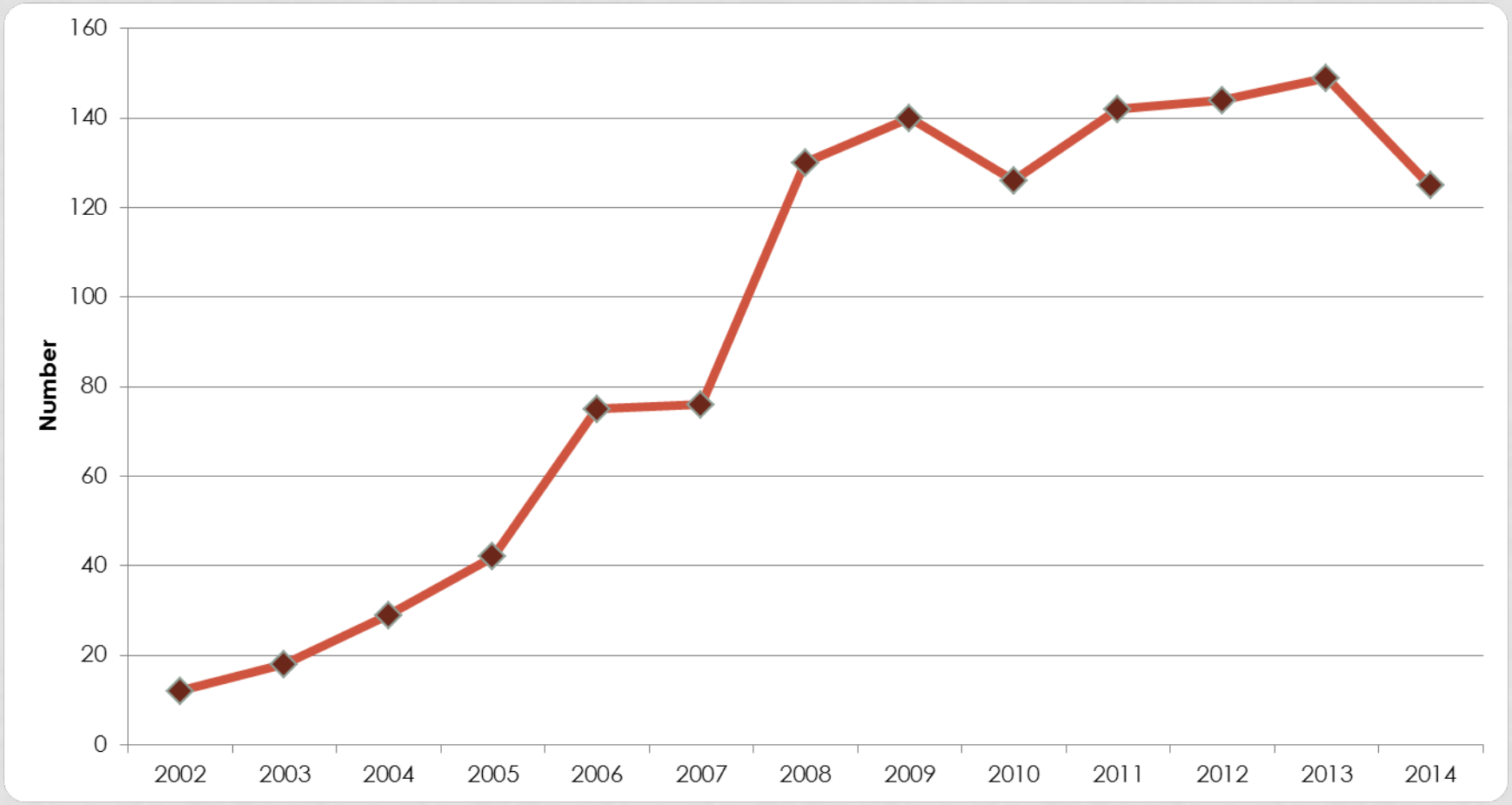
- First NeoMed clinic visit within 1 week of discharge
- Infants requiring medication for NAS are seen at least every 2 weeks
- Infants not requiring treatment follow up monthly for the first 4 months, then every 2-4 months until 12-18 months
- Bayley III Scales at 8-10 months
- Hepatitis C antibody at 18 months for exposed infants
- Multidisciplinary approach involving primary care provider, home health, early intervention, ChARM team, and maternal substance abuse provider

UVM Children's Hospital
Agree on methadone weaning plan

- Review symptoms of "withdrawal" if any
- "Usual weans"
  - 0.02 mg every Monday and Thursday OR
  - 0.02 mg every Monday
- Provide written schedule for the weaning
- If any change in weaning schedule – first discuss with clinic

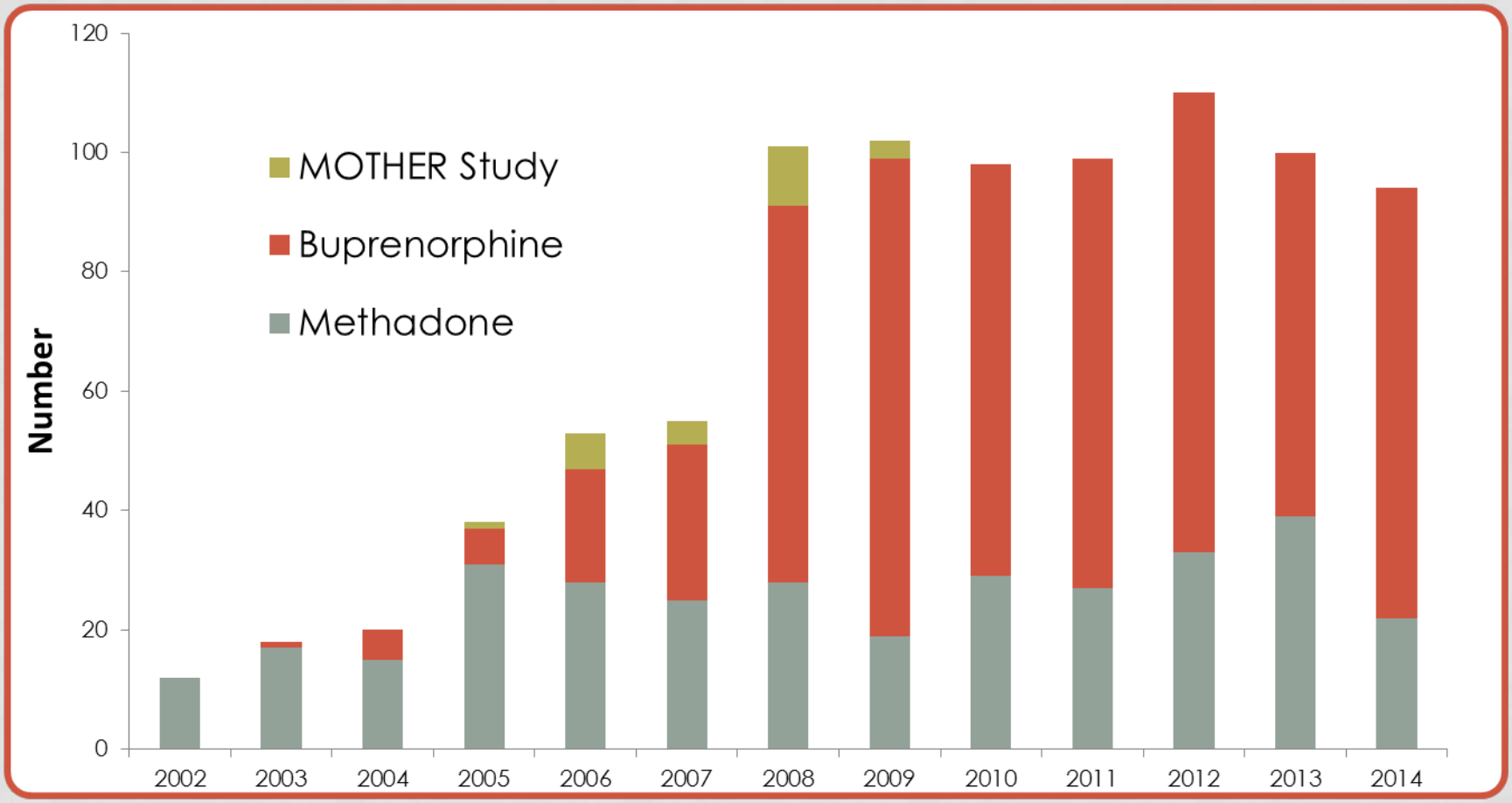
UVM Children's

Total Opioid-exposed Newborns Followed at UVM Children's Hospital(1,208 newborns)



UVM Children's Hospital:

Infants born to opioid dependent women with substance abuse on **methadone** or **buprenorphine** at delivery (N = 876)



UVM Children's Hospital

% Infants who received pharmacologic therapy

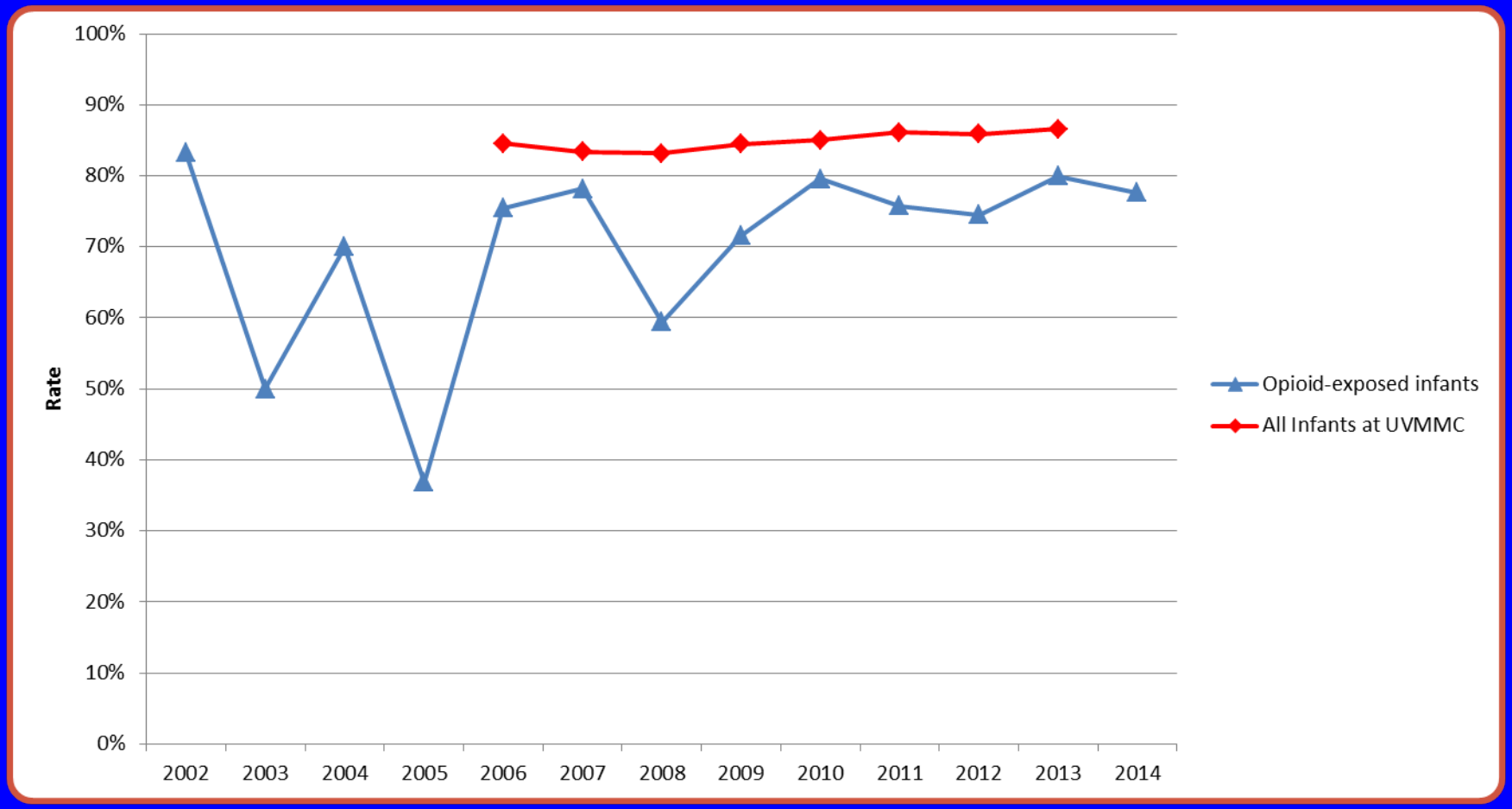
Why did pharmacologic treatment for NAS decrease?

- Better use of non-pharmacologic treatment
- Less subjectivity in NAS scoring
  - Through participating in MOTHER study
  - Decreased assumption of need for treatment
- Over time, the proportion of buprenorphine-treated pregnant women increased

Mean Length of Hospital Stay

Infants treated with outpatient methadone (UVM Children's Hospital)

UVM Children's Hospital
Breastfeeding at discharge



UVM Children's Hospital
Outcomes

- Average length of treatment: 3.2 months (2014)
- No infant deaths from methadone overdose
- Developmental outcomes on 166 children assessed at 7-14 months with the Bayley III scale mean percentiles > 50th%
- From 2000 to June 4th, 2015 there were 13 deaths / 1278 opioid-exposed infants (deaths < 2 years of age)
  - Shared sleeping: 7
  - Motor vehicle accidents: 2
  - Remainder (1 each): SIDS, congenital heart malformation, extreme prematurity, abusive head trauma

Vermont Experience: Overall

- ChARM Team: Children and Recovering Mothers
- Monthly multidisciplinary meetings with multiple agencies: impaneled
- High risk factors:
  - Increased distance to treatment center
  - Discontinuation of methadone / buprenorphine
  - Actively using partner
  - Abusive relationship with partner
- Women respond well to positive interactions with health care providers

methadone/buprenorphine treatment centers

Summary of NOWS

- NOWS is increasing in US with increase in healthcare $
- Behind every case of NOWS, there is a mother suffering from the disease of addiction – this is where efforts need to be the greatest!
- Several factors can contribute to NOWS severity
- Many scoring tools – none are truly validated
- Non-pharmacologic treatment can affect NOWS
- AAP endorses morphine or methadone for NOWS
- Developmental / behavioral outcomes are overall not affected by opioid-exposure in utero on its own, unlike alcohol exposure
- UVM has program which decreases length of stay and healthcare $ safely and effectively

Babyleavase.com

The health of the baby depends upon the mother’s health

Acknowledgements

I would like to thank the infants and families I have had the pleasure of caring for – I continue to learn from them daily.

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